Cardiac disease in beta-thalassaemia major: is it reversible?

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ABSTRACT

Introduction: The aim of this study was to evaluate the spectrum of cardiac involvement and its outcome in beta-thalassaemia major.

Methods: There were 75 patients with a mean age of 13.8 (+/- 5.5) years, of whom 33 were male and 42 were female. Clinical history, examination and laboratory investigations were assessed. Electrocardiograms, chest radiographs and echocardiograms were reviewed.

Results: 44 patients had cardiac involvement in the form of left ventricular systolic dysfunction in 17, diastolic dysfunction in 22, pericardial effusion in 12 and pulmonary hypertension in 12 patients. With intense chelation therapy and cardiac medications, the condition of 13 of 17 patients with systolic dysfunction, and four of 22 with diastolic dysfunction, improved.

Conclusion: Cardiac disease is a common complication of siderotic disease in thalassaemia major and it can be prevented with regular chelation. This study has shown improved systolic function after regular chelation therapy.

Keywords: cardiomyopathy, chelation, haemosiderosis, left ventricular dysfunction, thalassaemia major

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INTRODUCTION

Beta (β)-thalassaemia major is the most common haemolytic anaemia in children and adolescents, particularly in countries where consanguinity is highly prevalent[1]. These chronically-transfused patients, if not assiduously chelated, are at high risk for cardiac dysfunction. Cardiac disease is the major cause of death in these patients and even in the best of centres, one third dies by the age of 35 years[2]. In many patients, despite adequate chelation, cardiac pathology is still abnormal due to a combination of factors such as iron deposition, fibrosis, hypertrophy and structural effects of chronic anaemia[3]. We studied a large cohort of patients with β-thalassaemia major with the objective of finding out the spectrum of cardiac disease, and assessing the severity of iron overload, and reversibility of the disease and outcome.

METHODS

A retrospective review of patients with β-thalassaemia evaluated for cardiac disease from 1999-2004 was done. Out of a total of 267 patients suffering from β-thalassaemia major seen during the study period, 75 (28%) were referred for cardiac evaluation. The mean age at the time of referral was 13.8 ± 5.5 years (range 2-24 years). There were 33 males and 42 females. Clinical history included age at diagnosis, first blood transfusion, its frequency and conjunctive chelation therapy. Presence of exertional dyspnoea, palpitations, dependent oedema and previous splenectomy were noted. Family history of thalassaemia major and deaths due to it were sought. Clinical signs of cardiac disease included raised jugular venous pulses in the absence of anaemic cardiac failure, rate and regularity of pulse, presence of hypotension, hyperdynamic precordium, gallop rhythm, increased intensity of the second heart sound and presence of systolic murmur at the apex or lower left sternal edge.

Investigations to evaluate the effects of secondary haemosiderosis included levels of serum ferritin, thyroid stimulating hormone, parathormone, serum calcium, serum phosphorus, serum alkaline phosphatase and fasting blood glucose levels. Screening for transfusion-induced Hepatitis B and C was done in all patients. Cardiovascular investigations included electrocardiogram, chest radiograph and echocardiogram. Presence of prolonged QTc interval, conduction abnormalities and repolarisation abnormalities (ST segment, T wave changes) on electrocardiogram, cardiomegaly and pulmonary oedema on chest radiograph were noted.

Two-dimensional (2D), M-mode, colour flow

mapping and spectral Doppler echocardiography were done using a Sonos 5500 Philips echocardiography machine (Philips Medical Systems, Andover, MA, USA), with a 5 MHz transducer for children and 3.75 MHz for adult patients. Patients were examined in the parasternal long and short axis, and four chamber projections. Ejection fraction and fractional shortening were calculated as an average of the measurements in the parasternal long and short axis and from left ventricular volumes measured by the Simpson's method. Global systolic function was considered abnormal if the ejection fraction was less than 55% and the fractional shortening was below 27%[4]. Left ventricular diastolic function was defined by the pattern of transmitral inflow on Spectral Doppler interrogation, consisting of E/A ratio, E wave deceleration time and isovolumetric relaxation time[5,6]. Diastolic dysfunction was diagnosed when the E/A ratio was less than 1[6], deceleration time was more than 220 ms in adults and 180 ms in children[7], or the isovolumetric relaxation time was more than 65 ms in adults[7,8] or 55 ms or more in children[4]. Restrictive left ventricular function was diagnosed when the E/A ratio was more than 2.5 and the deceleration time of E wave was less than 110 ms[4,9].

Myocardial performance index, "the Tei index", was calculated by dividing the sum of isovolumetric contraction and relaxation times by the left ventricular ejection time[4,7,8], and this indicated the combined systolic and diastolic function of the myocardium. An average of three readings was taken for each parameter. The Tei index was considered abnormal if it was more than 0.46 (normal 0.38 ± 0.7 in children and 0.41 ± 0.05 in adults) in the left ventricle[4,8]. The presence of pericardial effusion was noted. the non-invasive estimate of pulmonary arterial pressures indicated by systolic pressure gradient across the tricuspid valve was also noted. Pulmonary hypertension was diagnosed if the peak systolic pressure gradient at the tricuspid valve was more than 30 mmHg[10].

Changes in management strategies after cardiac evaluation were noted. Short-term outcome of patients with cardiac disease was noted on clinical grounds as improved cardiac status, controlled but continued cardiac failure, uncontrolled cardiac failure and death. Echocardiography was repeated in 6-12 months' time in all patients diagnosed to have a cardiac disease. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 13.0 (Chicago, IL, USA). Frequencies, means and standard deviations were calculated by descriptive statistics. Uni-variate analysis with stepwise logistic regression and Mann-Whitney test (non-parametric) were performed to determine the factors related to cardiovascular disease. A p-value of <0.05 was considered to be significant.

Table I. Echocardiographical features in patients evaluated for cardiovascular disease.

Parameter	Number (%) of patients
Normal echocardiogram	31 (41)
Fractional shortening (<27%)	17 (23)
Ejection fraction (<55%)	17 (23)
Mitral E/A wave ratio <1	16 (21)
Mitral E/A wave ratio >2	18 (25)
Deceleration time >200 ms or 180 ms	12 (16)
Deceleration time <110 ms	10 (13)
Isovolumetric relaxation time >65 ms	16 (21)
Tei index >0.46	40 (52)
Peak gradient of TR >30 mmHg	12 (16)
Pericardial effusion	12 (16)
Patients with one/more abnormality	44 (59)
Improved cardiac disease on follow-up	17 (38)

Key: LV: left ventricle; TR: tricuspid regurgitation

RESULTS

Blood transfusion was started at a mean age of 1.1 ± 1.5 years (range 6 months - 9 years). Transfusion frequency was at a mean of 20.4 ± 10.9 days (range 3-90 days). Regular five nights per week chelation therapy with subcutaneous desferrioxamine therapy was practised by only 14 (18%) patients. Family history of thalassaemia major was present in 51 (68%) patients and family history of sibling death due to thalassaemia was present in 14 (19%) patients. Exertional dyspnoea, palpitations and pedal oedema were present in 27 (36%) patients. Signs of cardiac failure in the form of raised jugular venous pulse, S3 gallop rhythm, crepitations were noted in 13 (17%) patients and arrhythmias were seen in three (4%) patients. 17 (23%) patients had splenectomy.

The mean serum ferritin for the whole group was 7,019 ± 4,775 ng/ml (range 1,304-28,503 ng/ml). Extra cardiac evidence of iron overload was seen as hypocalcaemia, hypothyroidism and diabetes mellitus in 16 (22%), four (6%) and two (3%) patients, respectively. 17 (23%) patients had hepatitis B and 36 (48%) had hepatitis C. Electrocardiographical abnormalities found were prolonged QTc interval in 25 (33%) patients, left ventricular hypertrophy in 35 (47%), and ventricular ectopics in three (4%) patients, one of whom had couplets. 25 (33%) patients had repolarisation abnormalities with ST depression and flat T waves. Chest radiographs showed cardiomegaly in 40 (54%) and pulmonary oedema in seven (9%) patients. All patients with pulmonary oedema had myocardial dysfunction.

Table II. Factors related to cardiovascular disease.

Parameter	Groups		95% CI	p-value
	Cardiac	Non-cardiac		
Transfusion age (years)	1.1 ± 1.6	0.76 ± 0.68	-0.1895 – 0.9812	0.14
Transfusion frequency (days)	18 ± 6	21 ± 13	-3.2846 – 8.4658	0.24
Age at cardiac evaluation (years)	13.9 ± 5	13.8 ± 6	-2.36 – 2.305	0.95
Desferrioxamine doses (day interval between doses)	9.8 ± 9.5	6.3 ± 7.3	-8.38 – -1.38	0.03
Serum ferritin (ng/ml)	8,517 ± 5,449	5,871 ± 3,347	1,534 – 5,758	0.001
Ejection fraction (%)	57.3 ± 4.1	67.1 ± 6.7	-13.2 – -3.1	0.002
Tei index	0.51 ± 0.2	0.38 ± 0.1	5.28 – 0.1854	0.001

Echocardiographical abnormalities are summarised in Table I. 44 (59%) patients were found to have cardiac disease of which cardiomyopathy was the most common manifestation. 15 (20%) had a peak systolic pressure gradient across the tricuspid valve of more than 30 mmHg and out of these, six had pressures measuring more than 50 mmHg, reflecting significant pulmonary arterial hypertension. A univariate analysis to look at the outcome was made between the cardiac and non-cardiac groups (Table II). Statistically significant differences were found in desferrioxamine therapy, serum ferritin levels, ejection fraction and Tei index.

Treatment was altered in all patients diagnosed with a cardiac disease. Those with systolic dysfunction were prescribed angiotensin converting enzyme (ACE) inhibitor (either captopril or enalapril) and diuretics (furosemide and spironolactone, alone or in combination). Those with symptomatic diastolic dysfunction were prescribed beta-blockers (atenolol or carvedilol). One patient with pericardial effusion required pericardiocentesis because of myocardial compression. Patients with ventricular ectopic couplets were treated with beta-blockers. All patients had intensification of chelation therapy with deferrioxamine with five-days-a-week subcutaneous infusion and were vigilantly being followed for the same. Continuous intravenous infusion of desferrioxamine was not prescribed to any patient due to the cost factor.

Nine of 44 (20%) patients with cardiac disease died. 13 out of 17 (59%) patients with systolic left ventricular dysfunction and 4 out of 22 (18%) patients with diastolic dysfunction improved with cardiac medication and regular chelation therapy. Pericardial effusion resolved in all patients. Pulmonary hypertension improved in six out of 12 (50%) patients. The remaining patients are surviving on medical therapy with controlled symptoms. Of the non-cardiac group, three (10%) died due to septicaemia and liver failure from hepatitis B or C.

DISCUSSION

The pathophysiology of cardiopathy in β-thalassaemia major is complex and multifactorial. It may be related to anaemic heart failure, iron overload cardiomyopathy, acute infectious myocarditis, acute pericarditis, conduction abnormalities or right heart failure due to pulmonary haemosiderosis, alone or in combination[9-15]. Despite advancement in treatment, cardiac dysfunction remains the leading cause of death[3]. All the patients in our study had elevated serum ferritin. Iron overload in β-thalassaemia major is the combined outcome of excessive absorption and transfusional haemosiderosis. The plasma turnover is 10-15 times of the normal value and is caused by the wasteful, ineffective erythropoiesis of an enormously-expanded bone marrow. The resulting outpouring of catabolic iron exceeds the iron-binding capacity of transferrin and appears as non-transferrin plasma iron (NTPI).

NTPI is highly toxic due its ability to promote free radical formation through the Haber-Weiss reaction, resulting in perioxidative damage to membrane lipids and proteins[3]. The process of liberating of lysosomal enzymes, damages the cytoplasm of myocytes, resulting in cell death. Another organelle implicated in iron toxicity is the sarcolemmal membrane leading to loss of Na, K-ATPase activity. This impairs the Na/Ca exchange mechanism, partially causing the functional abnormalities noted in the iron-overloaded heart[15]. Finally, iron overload causes injury to the mitochondria, leading to a decrease in the mitochondrial respiratory complex activity[4], which may be responsible for cardiac disease in some patients.

The relationship of total body iron overload to iron deposition within the myocytes and the development of myocardial dysfunction remain perplexing, because some patients with advanced haemosiderosis of other organs have little myocardial deposition. In one study, conduction abnormalities correlated poorly with conduction tissue infiltration seen at autopsy

in patients who died of arrhythmias. Moreover, iron may cause reactive fibrosis or hypertrophy within the myocardium to account for the variable responses observed. Vogel et al hypothesised that iron deposition is predominantly in the interventricular septum in the early stages[16]. Iron deposition is mainly within the ventricles and can be patchy[2].

Pathophysiologically, iron overload cardiomyopathy is of a restrictive nature early in the disease process, manifesting as left ventricular diastolic dysfunction. However, as the disease progresses, systolic function also becomes impaired[3,11]. Davis et al[17] found that it is the systolic dysfunction that determines the outcome in most of the patients. In our series, 22 out of 44 (50%) patients had diastolic dysfunction and 17 out of 44 (39%) had systolic dysfunction, whereas 40 out of 44 (91%) patients had global myocardial dysfunction (abnormal Tei index). In the study done by Kremastinos et al, systolic dysfunction was related to infectious myocarditis that occurred in these children possibly due to their immunocompromised state[9]. Right ventricular failure is less frequent and is due to right ventricular cardiomyopathy or pulmonary hypertension secondary to pulmonary haemosiderosis[14]. Pericardial effusion, seen in 12 of our patients, is a poorly-understood complication and is possibly related to restrictive cardiomyopathy or acute infectious pericarditis[18,19]. Iron-overloaded hearts are vulnerable to conduction abnormalities and arrhythmias as shown in animal models, suggesting abnormality in conduction of action potential in the whole heart[20].

Desferrioxamine (DFX) is the most effective and safest iron chelator for prevention and treatment of iron overload cardiopathy. Non-compliance to DFX therapy was the cause for the very high iron overload seen in our patients. Although intravenous therapy has been recommended by several authors for cardiac disease, DFX is more easily given by intermittent subcutaneous infusion for 8-12 hours a day on 4-6 days a week, using a battery-operated pump[21,22]. Subcutaneous infusion was prescribed to our patients on domiciliary basis. Anderson et al have shown reversibility of heart failure with regular DFX therapy[23]. In our study, 13 out of 17 (76%) patients with systolic dysfunction and four out of 22 (18%) with diastolic left ventricular dysfunction showed improvement.

Iron-overload cardiac disease in patients with β-thalassaemia major is often fatal. Diastolic left ventricular dysfunction develops early, but most patients die of systolic dysfunction. In our series, non-compliance to DFX therapy was the cause of this devastating complication. However, with regular chelation and anticongestive therapy, the systolic dysfunction was seen to improve, thus providing a good reason for all taking care of these children to continue with intense chelation.

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